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PHARMACOKINETICS AND DISPOSITION

St John's wort extract (Ze 117) does not alter the pharmacokinetics of a low-dose oral contraceptive

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Abstract

Purpose St John's wort (*Hypericum perforatum*) is an herbal remedy that is widely used in the treatment of depression. Recent clinical data have demonstrated that St John's wort extracts interfere with the action of various drugs and possibly also with combined oral contraceptives. Therefore, we investigated the effects of a St John's wort extract (Ze 117) with low hyperforin content on the pharmacokinetics of ethinylestradiol and 3-ketodesogestrel.

Method Sixteen healthy female volunteers, who had taken a low-dose oral contraceptive (Lovelle contains 0.02 mg ethinylestradiol + 0.15 mg desogestrel) for at least 3 months, participated in the study. Pharmacokinetic data (AUC, C_{\max} , t_{\max}) were determined the day before (reference)

and after (test) a 14-day period of Ze 117 intake (250 mg twice daily).

Results Before the co-administration of Ze 117 on day 7, the geometric mean (geometric coefficient of variation) for the AUC_{0-24} of ethinylestradiol was 152.53 pg·h/ml (87.39%) and after co-administration on day 21 it was 196.57 pg·h/ml (78.14%). The respective values for ketodesogestrel were 36.37 pg·h/ml (34.18%) and 41.12 pg·h/ml (34.36%). The mean of individual ratios (reference-to-test) of log-transformed AUC values (90% confidence interval) were 0.951 (0.915–0.986) for ethinylestradiol and 0.968 (0.944–0.992) for ketodesogestrel indicating a small loss in bioavailability, but bioequivalence nevertheless.

Conclusion These results indicate that the recommended dose of the hypericum extract Ze117, which has a low hyperforin content, does not interact with the pharmacokinetics of the hormonal components of the low-dose oral contraceptive.

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Keywords Ze 117 · *Hypericum perforatum* · St John's wort · Hyperforin · Ethinylestradiol · 3-Ketodesogestrel · Interaction

Introduction

Extracts of St John's wort are widely used in the treatment of mild to moderate depression [1]. They are popular because of their herbal origin, their good tolerance and their over-the-counter availability.

Adverse events that occurred when formulations of St John's wort were taken concomitantly with other drugs, such as digoxin [2], phenprocoumon [3], theophylline [4], amitriptyline and nortriptyline [5], cyclosporine [6] and

indinavir [7], have in the past cast doubt on the safety of this compound and on its suitability for self-medication. These occurrences led regulatory authorities to take precautionary measures [8] and investigators to study interactions of St John's wort with other drugs and the possible mechanisms of these interactions. The St John's wort preparations on the market differ considerably in composition and dosage, which is the reason why study results are only valid for the product under investigation [9–13]. The extract Ze 117 used in this study is standardised to 0.2% hypericin and is characterised by its low content of hyperforin [10, 14]. The recommended daily dosage is 500 mg, which is well documented to be clinically efficient in cases of mild to moderate depression [15–17].

The cytochrome P450 (CYP) family of drug metabolizing enzymes [18–21] is very likely a hypericum-drug interaction site, among others (e.g. the P-glycoprotein drug transporters). Changes in enzymatic activity would affect pharmacokinetics considerably.

St John's wort extracts have been accused of interacting with the hormonal components of oral contraceptives, thus causing spotting or break-through bleeding [22–26]. However, current research seems to put these results into perspective when differentiating St John's wort preparations by their hyperforin content [13, 27–29]. Our study was carried out to investigate the effects of a specific St John's wort extract (Ze 117) on the pharmacokinetics of ethinylestradiol and 3-ketodesogestrel, which are the two pharmacologically effective components of the low-dose contraceptive Lovelle.

Methods

Volunteers

Sixteen healthy female volunteers (Caucasian) were enrolled in the study. All participants had taken the oral contraceptive Lovelle (Organon, Oberschleissheim, Germany) for at least 3 months. They had not received any other medication during the 3 weeks prior to the study. All volunteers were clinically healthy with a body mass index (BMI) within -10 to $+20\%$ of the norm. Pregnancy was excluded in all volunteers using the β -HcG immunoassay "viola-c" (CARE Diagnostika, Moellersdorf, Austria). They were advised to additionally use a mechanical method to exclude conception during the study period. Since this was intended as a pilot trial, a formal sample size estimation was not done. The study was approved by the Ethics Committee at the Free University of Berlin, University Medical Centre Benjamin Franklin. All participants gave their written informed consent prior to the study start.

Study design

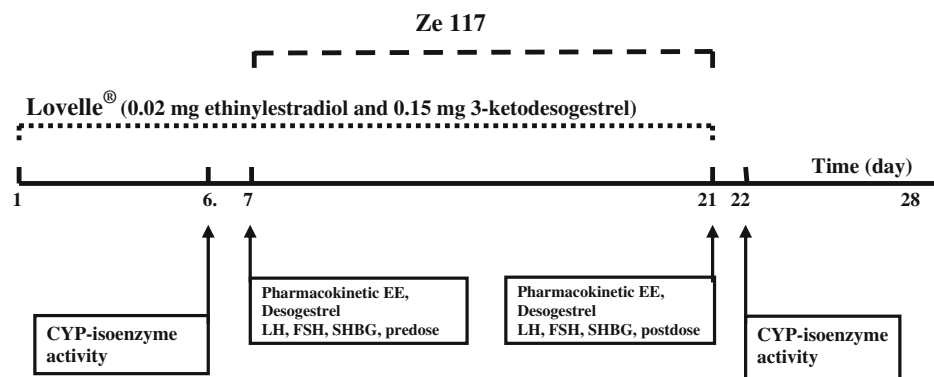
Tablets containing 250 mg of the dry extract Ze 117 were administered twice daily, in the morning and evening. [Ze 117: Remotiv, Zeller AG, Romanshorn, Switzerland; drug extract ratio 4–7:1, ethanol 50% (V/V), standardised hypericin content 0.2% (1 mg in the daily dose) and hyperforin content $\leq 0.2\%$ (≤ 1 mg in the daily dose)]. The actual hyperforin content in lot no. 964361 used for this study was 0.13%, i.e. 0.65 mg in the daily dose. Ze 117 medication was initiated on day 7 and finished on day 21 of the Lovelle administration scheme (Fig. 1). Blood samples were taken on day 7 and 14 of Ze 117 dosing. The amounts of hypericin and pseudohypericin in these samples were determined in order to verify volunteer compliance. Determinations were performed with a validated HPLC method [30].

Lovelle (contains 0.02 mg ethinylestradiol + 0.15 mg desogestrel) was administered from day 1 to day 21, as described in the package insert (lot 476701; Organon, Oberschleissheim). To assess the pharmacokinetic parameters of Lovelle, the volunteers were hospitalised for 1 day and an indwelling catheter was placed intravenously. Food intake was standardised. Blood samples were taken before intake (0 min) and then after 20 min, 40 min, 1 h, 1 h 15 min, 1 h 30 min, 1 h 45 min, 2 h, 2 h 30 min, 3 h, 4 h, 5 h, 6 h, 8 h, 10 h, 12 h and 24 h. Serum samples were centrifuged and 2-ml serum samples were frozen (-20°C) as duplicates. Determination of serum ethinylestradiol and 3-ketodesogestrel was performed using a liquid chromatography-mass spectrometer assay. Assays were carried out by the commercial analytical laboratory Analytisches Zentrum Biopharm (Bitterfelder Strasse 19, D-12681 Berlin, Germany).

3-Ketodesogestrel

Analyte and internal standard were separated from serum by liquid/liquid extraction with 5 ml pentane. The analyte concentration was determined by reversed-phase chromatography [column: YMC-Pack Octyl, 150×3 mm, $5 \mu\text{m}$; eluent 30% (v/v) 0.1 M ammonium acetate/70% (v/v) methanol] with mass selective detection (SIM ion: 325.00, fragmentor: 100]. The working conditions of the spray chamber were as follows: gas temperature 200°C , drying gas 12 l/min, neb press 55 psig, vcap 3,400 V. The equipment (series 1100, 1100 MSD instruments) was purchased from Agilent Technologies (Santa Clara, CA, USA). The lower limit of quantification was 0.2 ng ml^{-1} for 3-ketodesogestrel. The intra-assay variability showed an imprecision between 7.66% (at 0.2 ng ml^{-1}) and 9.87% (at 6 ng ml^{-1}) and an inter-assay variability between 3.90% (at 0.2 ng ml^{-1}) and 3.39% (at 6 ng ml^{-1}) for 3-ketodesogestrel.

Fig. 1 Study design



($n=6$). The method was validated over the range 0.2–6 ng/ml for 3-ketodesogestrel.

Ethinylestradiol

Analyte and internal standard were separated from serum by extraction. Into Nexus cartridges containing 1 ml of the sample, 15 μ l of working solution of the internal standard (ethinylestradiol-2,4,16,16- d_4) was added. The cartridges were washed with 1 ml of 5% methanol, dried and extracted with hexane/ethyl acetate (1:4, v/v). The eluate was collected in sample vials.

The extraction was followed by a specific derivatisation process. For this purpose 500 μ l water and 20 μ l methyl orange solution were added to the eluate and centrifuged. The upper phase was separated and evaporated. The residue was dissolved in a mixture of triethylamine and pentafluorobenzoyl chloride solutions. After evaporation, ethylacetate together with *N*-methyl-*N*-(trimethylsilyl) trifluoroacetamide (MSTFA) was added. After incubation for 20 min at 60°C the solvent was evaporated, and 200 μ l water, 20 μ l methylorange and 340 μ l hexan were added. This process rendered ethinylestradiol measurable by gas chromatography and mass selective detection. Ethinylestradiol was measured by GC-MS. The lower limit of quantification was 8 pg ml⁻¹ for ethinylestradiol. The intra-assay variability showed an imprecision between 16.22% (at 8 pg ml⁻¹) and 5.76% (at 170 pg ml⁻¹) and an inter-assay variability between 10.38% (at 8 pg ml⁻¹) and 4.23% (at 170 pg ml⁻¹) for ethinylestradiol ($n=6$). The method was validated over the range 8–170 pg ml⁻¹ for ethinylestradiol.

CYP enzyme phenotyping

On day 6 of the Lovelle administration scheme and on the day following the last administration of Ze 117, phenotyping for cytochrome P450 enzymes CYP2D6 and CYP2C19 and evaluation of CYP3A4 activity were carried out, since these P450 enzymes are involved in the metabolism of the

Lovelle components. For the phenotyping of CYP2D6, the dextromethorphan test was used. Dextromethorphan is metabolised by CYP2D6 to dextrorphan. After glucuronidation, the metabolite is excreted by the kidneys. The ratio was determined in the urine that had been collected during the 5 h following a single dose of dextromethorphan, since any interval between 4 and 12 h is feasible for determining the metabolic ratio [31]. For incubation, 500 μ l of urine was mixed with 500 μ l of β -glucuronidase solution (type H5, 5,000,000 units dissolved in 50 ml 0.2 M sodium acetate buffer, pH 5.0). After incubation, dextromethorphan and dextrorphan were quantified by HPLC with fluorescence detection [32]. The lower limits of quantification for dextromethorphan and dextrorphan were 0.01 and 0.1 μ g ml⁻¹ for 500 μ l of assayed human urine, estimated at the three-fold value of the baseline noise level. The method was validated for the linear range 0.01–2.0 μ g ml⁻¹ for dextromethorphan and 0.1–20 μ g ml⁻¹ for dextrorphan using 500 μ l of urine.

The omeprazole test [33] was used for the phenotyping of CYP2C19 and for the evaluation of CYP3A4 activity. The latter is possible because St John's wort increases CYP 3A4 exclusively, while CYP3A5 and CYP3A43 remain unaffected and CYP3A7 decreases [34]. Omeprazole is metabolized by CYP2C19 to 5'-hydroxy-omeprazole and by CYP3A4 to omeprazole-sulphone [35]. The metabolic ratio of the total omeprazole + sulphone metabolite to 5'-hydroxylated omeprazole is the parameter that characterises the CYP2C19 phenotype. It is above 12 in poor metabolizers and below 12 in extensive metabolizers [33]. Omeprazole and its metabolites 5-hydroxy-omeprazole and omeprazole-sulphone were analysed by HPLC with UV detection in plasma samples taken 3 h after omeprazole administration.

For phenotyping, volunteers spent half a day in-house. After emptying their bladder, they took the medication under the supervision of a nurse between 6.45–7.15 a.m. (30 mg dextromethorphan hydrochloride, Hustenstiller Ratiopharm, lot 4356B7, Ratiopharm, Ulm, Germany and 40 mg omeprazole magnesium, Antra MUPS, lot

AE 3032, ASTRA, Wedel, Germany). Urine was collected for three periods: 0–5, 5–8 and 8–24 h (at home). From these three samples, aliquots of 20 ml were frozen and the remaining amounts were used for a 24-h sample, from which aliquots of 20 ml were frozen as well. Blood sampling was carried out via an indwelling vein catheter, and 3 h after drug administration an EDTA blood sample was taken for analysis. The parent compounds and the related metabolites were determined by validated HPLC methods [33].

FSH, LH and SHBG

Serum concentrations of follicle-stimulating hormone (FSH), luteinising hormone (LH) and sex-hormone-binding globulin (SHBG) were determined in blood samples that had been taken on the day prior to the first (day 7) and on the day after the last Ze 117 administration (day 21). The following commercial kits were used: FSH ELISA (EIA-1288), LH (Serum) ELISA (EIA-1289) and SHBG MTPL (EIA-1567), purchased from DRG Instruments (Marburg, Germany).

Hypericin and pseudohypericin

To check volunteer compliance, the St John's wort components hypericin and pseudohypericin were determined in plasma samples from all participants taken at day 7 and day 14 of the co-administration by isocratic reversed-phase HPLC with fluorescence detection after liquid-liquid extraction. The limit of quantification was 0.25 ng ml^{-1} for hypericin and pseudohypericin [30]. The blood samples were taken 12 h after the last Ze 117 administration and referred therefore to the trough values.

Pharmacokinetic data and statistics

The following pharmacokinetic parameters of ethinylestradiol and 3-ketodesogestrel were determined for each of the 16 volunteers: area under the concentration time curve (AUC_{0-24}), measured maximum peak concentration (C_{max}) and observed peak time (t_{max}). For these calculations, the programs STATA 10 and BioEqV1.2, which had been validated by control calculations with literature data sets, were used. The bioavailability data for ethinylestradiol and 3-ketodesogestrel were tested by calculating the quotient of the AUC_{0-24} and C_{max} before and after the 2 weeks of co-administration of Ze 117.

For phenotyping, the comparative data of FSH, LH and SHBG, as well as hypericin/pseudohypericin differences, were tested using the non-parametric Wilcoxon test for matched pairs. *P*-values of $\leq 5\%$ were considered significant.

For the assessment of bioequivalence, AUC_{0-24} and C_{max} values were log-transformed and the means of individual ratios (reference-to-test) and the 90% confidence intervals were calculated (SPSS for Windows, version 15.0). Bioequivalence was assumed when the 90% confidence intervals were completely included in the interval of -80 to 125% . Data on AUC_{0-24} and C_{max} were reported as arithmetic as well as geometric means and geometric coefficients of variation. For t_{max} , values were compared between reference and test by using the non-parametric Wilcoxon signed-rank test.

Results

The study population consisted of volunteers aged 31.8 ± 8.2 years with a weight of $66.5 \pm 11.9 \text{ kg}$ and a BMI of $23.8 \pm 4.2 \text{ kg/m}^2$. The two diagrams in Fig. 2 show the

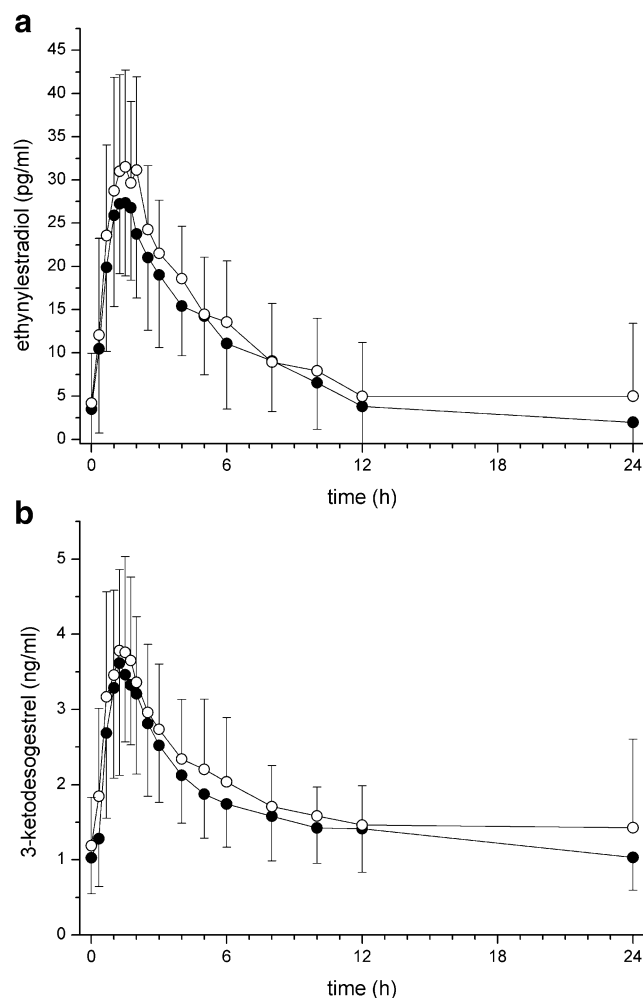


Fig. 2 Mean (\pm SD) serum concentrations of ethinylestradiol (**a**) and of 3-ketodesogestrel (**b**) ($n=16$). Open circles indicate the baseline, closed circles indicate values after 14 days of application of Ze 117

Table 1 Pharmacokinetic parameters of ethinylestradiol and 3-ketodesogestrel ($n=16$)

	Day 7			Day 21			Ratio day 7-to-day 21 (90% CI)
	Arithm. mean	Geom. mean (CV%)	Median (range)	Arithm. mean	Geom. mean (CV%)	Median (range)	
Ethinylestradiol							
AUC _{0–24} (pg h/ml)	188.14	152.53 (87.39)	–	235.73	196.57 (78.14)	–	0.951 (0.915–0.986)
C _{max} (pg/ml)	32.40	30.45 (39.40)	–	36.68	34.42 (41.53)	–	0.968 (0.939–0.997)
T _{max} (h)	–	–	1.25 (0.67–2.50)	–	–	1.50 (0.67–2.00) NS	–
3-Ketodesogestrel							
AUC _{0–24} (pg h/ml)	38.27	36.37 (34.18)	–	43.38	41.12 (34.36)	–	0.968 (0.944–0.992)
C _{max} (pg/ml)	4.30	4.09 (34.31)	–	4.40	4.25 (28.29)	–	0.983 (0.893–1.073)
T _{max} (h)	–	–	4.70 (1.07–5.85)	–	–	4.58 (0.92–5.21) NS	–

90% CI 90% Confidence interval of individual ratios of log-transformed values, NS not significantly different from day 7 (two-sided Wilcoxon signed ranks test), *arithm. mean* arithmetic mean, *geom. mean* geometric mean, *CV%* geometric coefficient of variation (%), *day 7* before application of Ze 117, *day 21* after 14 days of ZE 117 application

mean serum concentrations of ethinylestradiol and 3-ketodesogestrel on day 7 and day 21 respectively, i.e. before and after 14 days of co-medication with Ze 117. The mean values for the pharmacokinetic parameters of ethinylestradiol and 3-ketodesogestrel are given in Table 1. The mean relative bioavailability ratios of the parameters C_{max} and AUC_{0–24} on day 21 increased by approximately 10% in comparison to day 7. The 90% confidence intervals of C_{max} and AUC_{0–24} remained within the usually accepted equivalence limits of 20%. Therefore, the serum concentrations of ethinylestradiol and 3-ketodesogestrel were equivalent on the two study days.

Serum FSH, LH and SHBG were analysed before and after intake of Ze 117 (Table 2). The value for LH was significantly less on day 21. FSH was also less, but not significantly. SHBG was significantly elevated on day 21.

All subjects were extensive metabolizers for CYP2D6 and CYP2C19. Co-medication with Ze 117 did not elicit any differences (Table 3). The activity of CYP3A4 was not

influenced by co-medication with Ze 117. Compliance control by way of hypericin and pseudohypericin plasma concentrations (Table 4) revealed that all subjects had taken the Ze 117 tablets regularly.

Adverse events were not reported, in particular no break-through bleeding or spotting.

Discussion

The interaction discussion related to St John's wort was initiated because of reports of break-through bleeding and spotting [22, 23]. There are studies which clearly indicate an interaction potential of St John's wort extracts with oral contraceptives [24–26]. The extracts administered in these studies were methanolic (80%), containing high amounts of hyperforin (20–35 mg) and dosed as 900 mg daily. In contrast, the present study demonstrates that the St John's wort extract Ze 117 neither induced break-through bleeding

Table 2 Mean serum concentrations of LH, FSH and SHBG (mean ± SD)

	LH (mIU/ml)	FSH (mIU/l)	SHBG (nmol/l)
Day 7 (Lovelie intake), before Ze 117 application	7.0±5.9	2.6±1.5	289.7±90.8
Day 21 (Lovelie intake), after last Ze 117 application	3.6±2.5	2.1±1.9	319.8±101.8
P-value	0.0009	0.0927	0.0318
Wilcoxon signed-rank test (day 7 vs. day 21)	*	NS	*

* $P<0.05$

NS Not significant

Table 3 Mean±SD molar ratios of parent substances to metabolites of three CYP enzymes

	Molar ratio		
	CYP2C19	CYP3A4	CYP2D6
Day 7, before Ze 117 application	4.5±2.8	6.5±2.6	0.004±0.004
Day 14, after Ze 117 application	4.2±2.5	6.5±2.4	0.003±0.005
Wilcoxon signed-rank test	0.900	0.875	0.317
Before vs. after Ze 117	NS	NS	NS

NS Not significant

or spotting, nor caused an interaction with the low-dose oral contraceptive Lovelle. The extract Ze 117 is extracted with ethanol (50%), and it contains less than 1 mg hyperforin in the daily dosage, which is set at 500 mg. Interestingly, when the identical low-dose oral contraceptive Lovelle was tested with Li 160 (600–900 mg extract, 18–27 mg hyperforin), the progestin component was significantly reduced [24]. The basic difference between both the extracts is their amount of hyperforin.

Drug-drug interactions are most likely attributable to ethinylestradiol, since it is the subject of different interaction mechanisms [36]. Nevertheless, Ze 117 co-medication did not affect the pharmacokinetic data of ethinylestradiol in this study. The pharmacokinetics of 3-ketodesogestrel, which requires bioactivation by CYP2D6 and CYP2C19 [37], was also not influenced by Ze 117. This observation is supported by the phenotyping data, which showed no differences in CYP2D6 and CYP2C19 activity before and after Ze 117 medication.

Contraceptives diminish the levels of FSH and LH, which results in the metabolic suppression of ovarian function and increased SHBG production in the liver [38, 39]. The reported changes in FSH, LH and SHBG reflect maintenance of this contraceptive action. Similarly, the pharmacokinetic data of the two Lovelle components were obviously not affected, since they behaved as reported under control conditions, i.e. the AUC was elevated to some extent on day 21 [40, 41].

Table 4 Mean±SD concentration values for hypericin and pseudohypericin on day 14 and 21

	Day 14 (1 week Ze 117)	Day 21 (2 weeks Ze 117)
Hypericin (ng ml ⁻¹)	2.7±1.2	2.9±1.2
Pseudohypericin (ng ml ⁻¹)	2.3±1.5	1.8±0.9

Drug-drug interactions may be related to the composition of the extract, to the daily dosage and to the duration of co-medication. Unchanged activity of CYP2D6 and CYP3A4 was reported when St John's wort had been taken for only 3 days [42] and 7 days [43], whereas an approximate doubling of CYP 3A4 activity was observed after 14 days [21]. Therefore, the 2-week period of co-medication with Ze 117 in the present study seems long enough to disclose any interaction, since induction of gene expression usually occurs within 48 h, and effects on drug serum concentrations are seen after 10 days at the latest [2, 21].

The St John's wort extracts associated with interactions with oral contraceptives were standardised to 0.3% hypericin and were taken in daily doses of 900 mg, which amounts to 2.7 mg hypericin and between 25 and 33 mg hyperforin per day [22–26]. However, Ze 117 is standardised to 0.2% hypericin. The daily dose of 500 mg extract, which has been proven to be efficient [15–17], contains 1 mg hypericin and less than 1 mg hyperforin (in this study 0.65 mg). The lower daily hyperforin intake could be the reason for the lack of interaction of Ze 117 with Lovelle pharmacokinetics. Also, intra-cyclic bleeding was more frequently reported for St John's wort extracts with higher hyperforin contents, including the extract Li 160 at a daily dosage of 600 mg [24]. This was not observed at all with Ze 117 at the recommended dosage of 500 mg extract; however higher doses have not been tested so far.

St John's wort extract with high hyperforin content significantly influenced the pharmacokinetic behaviour of cyclosporine. However, after removing hyperforin, this drug-drug interaction was abolished, indicating that the interaction was related to hyperforin [13]. In another clinical trial, a different St John's wort extract with low hyperforin (3.5 mg hyperforin in the daily dose) did not influence the pharmacokinetic behaviours of alprazolam, caffeine, tolbutamide or digoxin [27]. The pharmacokinetic behaviour of midazolam also correlated dose-dependently with hyperforin content and differed among the investigated products [44]. The systematic review of 31 prospective clinical trials by Whitten et al. [28] concluded that low-dose hyperforin extracts (<4 mg/day) do not demonstrate a significant effect on CYP3A.

Although a small decrease in ethinylestradiol and 3-ketodesogestrel was observed in the present study, the effect was not significant. AUC_{0–24} and C_{max} were bioequivalent before and after a 14-day application of Ze 117.

In conclusion, the intake of reduced-hyperforin St John's wort preparations is less likely to interact with drugs and may substantially lower the risk of serious herb-drug interactions.

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